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Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation risk $\geq 5\%$ or Framingham risk $>20\%$: post hoc analyses of the JUPITER trial requested by European health authorities

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Aims

On the basis of the JUPITER trial, European health authorities recently approved the use of rosuvastatin to reduce first major cardiovascular events among 'high' global risk primary prevention patients defined either by Framingham risk score $>20\%$ or European systematic coronary risk evaluation (SCORE) $\geq 5\%$. However, as these are *post hoc* analyses, data describing these subgroups have not previously been available to the clinical community.

Methods and results

We randomized 17 802 apparently healthy men aged ≥ 50 and women ≥ 60 with low-density lipoprotein cholesterol (LDL-C) <3.4 mmol/L, who were at an increased vascular risk due to elevated levels of C-reactive protein measured with a high-sensitivity (hs) assay to rosuvastatin 20 mg daily or placebo. Patients with high global cardiovascular risk at baseline were identified by 10-year Framingham risk score $>20\%$ or SCORE risk $\geq 5\%$. During 1.8-year median follow-up (maximum 5 years) of patients with Framingham risk $>20\%$, the rate of myocardial infarction/stroke/cardiovascular death was 9.4 and 18.2 per 1000 person-years in rosuvastatin and placebo-allocated patients, respectively [hazard ratio (HR): 0.50, 95% confidence interval (CI): 0.27–0.93, $P = 0.028$]. Among patients with SCORE risk $\geq 5\%$, the corresponding rates were 6.9 and 12.0 using a model extrapolating risk for age ≥ 65 years (HR: 0.57, 95% CI: 0.43–0.78, $P = 0.0003$) and rates were 5.9 and 12.7 when risk for age was capped at 65 years (HR: 0.47, 95% CI: 0.32–0.68, $P < 0.0001$).

Conclusion

In primary prevention patients with elevated hs C-reactive protein who have high global cardiovascular risk (10-year Framingham risk score $>20\%$ or SCORE risk $\geq 5\%$), but LDL-C levels not requiring pharmacologic treatment, rosuvastatin 20 mg significantly reduced major cardiovascular events.

ClinicalTrials.gov Identifier: NCT00239681

Keywords

Rosuvastatin • Coronary heart disease • C-reactive protein • High risk

Introduction

The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to

investigate whether rosuvastatin decreased first major cardiovascular events among patients with levels of low-density lipoprotein cholesterol (LDL-C) <3.4 mmol/L (130 mg/dL), but who were at increased cardiovascular risk due to elevated levels of

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high-sensitivity (hs) C-reactive protein.¹ As previously reported, after median follow-up of 1.9 years (maximum 5 years), rosuvastatin use was associated with a 54% reduction in myocardial infarction (MI), a 48% reduction in stroke, a 46% reduction in revascularization, a 43% reduction in venous thromboembolism, and a 20% reduction in total mortality.^{1,2} On this basis, the United States Food and Drug Administration approved the use of rosuvastatin for primary prevention of cardiovascular events among JUPITER eligible participants with elevated hs C-reactive protein and at least one additional risk factor.³ In contrast, the Dutch Medical Agency (the MEB) and 18 other European health authorities have approved rosuvastatin for the subgroup of trial participants who were considered to be at 'high risk' either on the basis of an estimated 10-year Framingham risk score >20% or an estimated systematic coronary risk evaluation (SCORE) risk of $\geq 5\%$.⁴ As neither of these criteria were used in the design of the JUPITER trial, these *post hoc* data, not published previously, are likely to be of utility for European practitioners and are thus presented here.

Methods

JUPITER was a double-blind, placebo-controlled trial which randomized apparently healthy men aged ≥ 50 and women aged ≥ 60 , with LDL-C <3.4 mmol/L (130 mg/dL) and C-reactive protein ≥ 2 mg/L in 26 countries. Participants did not qualify for statin therapy according to guidelines in effect in 2003, but were at increased cardiovascular risk due to evidence of systemic inflammation.⁵

Full details of the trial protocol, procedures, and methods of confirming clinical endpoints and ascertaining adverse events have been presented previously.^{1,6} Trial exclusion criteria included use within 6 weeks before screening of any lipid-lowering therapies, the current use of post-menopausal hormone replacement therapy, evidence of hepatic dysfunction, serum creatinine >177 μ mol/L, diabetes mellitus, prior cardiovascular or cerebrovascular events, chronic inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease, or other serious medical conditions that might compromise safety or successful completion of the study.

Potentially eligible subjects underwent a 4-week placebo run-in phase; those with compliance >80% were randomly allocated to rosuvastatin 20 mg daily or placebo and followed for occurrence of the primary endpoint, a composite of MI, stroke, arterial revascularization, unstable angina, or confirmed death from cardiovascular causes. An independent endpoint committee adjudicated primary endpoint events. Evaluation of all-cause mortality, MI/stroke/cardiovascular death, fatal/non-fatal MI, and fatal/non-fatal stroke was pre-specified.

The trial's monitoring plan called for two interim efficacy analyses with the O'Brien–Fleming stopping boundaries determined by means of the Lan–DeMets approach. The stopping boundary was crossed at the first planned efficacy evaluation, and on 29 March 2008, the independent data and safety monitoring board recommended termination of the trial. The steering committee accepted that recommendation and only major cardiovascular events occurring prior to 30 March 2008 are included in this analysis. Reporting of adverse events and all-cause mortality continued in a blinded manner until each participant appeared for a closeout visit and discontinued study medication.

Clinic physicians reported adverse events as verbatim terms, which were coded to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms⁷ by an automated system, over-read by trained

coders. We report here treatment-emergent adverse events, i.e. events that either began or worsened after randomization.

Participants provided fasting blood samples for lipid profiles at baseline, annually thereafter, and at the final visit. Alanine aminotransferase was measured at baseline, 3 and 6 months after randomization, semi-annually thereafter, and at the final visit. Serum creatinine was measured at baseline, 1 year after randomization, and at the final visit. We estimated glomerular filtration rate by the Modification of Diet in Renal Disease study equation.⁸

Statistical analyses

For consistency with *post hoc* analyses performed for the European health authorities, all study participants were classified according to 10-year global risk estimates using the Framingham risk score⁹ and the European SCORE risk algorithm.¹⁰ The Framingham risk score estimates the 10-year risk of MI/coronary death on the basis of age, gender, smoking status, blood pressure, and total and high-density lipoprotein cholesterol (HDL-C), whereas the SCORE algorithm estimates the global 10-year risk of cardiovascular death on the basis of age, gender, smoking status, systolic blood pressure, total cholesterol, and geographic region. The regional risk was based on each participant's country of enrolment; those enrolled in Belgium, Canada, Chile, Israel, Mexico, the Netherlands, and Switzerland were categorized as low risk. Patients enrolled in Argentina, Brazil, Bulgaria, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Norway, Panama, Poland, Romania, Russia, South Africa, UK, USA, Uruguay, and Venezuela were categorized as high risk.

The SCORE model is limited to ages 45–64 years. To account for the large proportion of subjects enrolled in JUPITER older than 65 years ($n = 10\,237$), a modification of the SCORE model was used in which the risk conferred by age was extrapolated for patients aged 65 or older (extrapolated model). Extrapolation was based on the contribution of age to the risk of cardiovascular death as assessed in the algorithm for patients up to 65 years of age. The extrapolated model is the model cited in the European CRESTOR Summary of the Product Characteristics.⁴ An analysis was also performed using the SCORE algorithm capped at 65 years (capped model), in which all subjects 65 years or older were assigned the risk of a 64-year old. This more conservative approach resulted in fewer patients being classified as high risk; 52% of the JUPITER participants had SCORE risk $\geq 5\%$ using the extrapolated model compared with 35% using the capped model. Analyses for patients with SCORE risk <5% are included as Supplemental data.

Analyses were performed on an intention-to-treat basis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated from the Cox proportional hazard models. Changes in lipoproteins and hs C-reactive protein levels were compared by the Wilcoxon signed-rank test. Baseline hs C-reactive protein is the mean of each participant's values at the screening and randomization visits. Analyses were performed using SAS version 8.2 (SAS Institute, Inc., Cary, NC, USA).

Results

JUPITER enrolled 17 802 men and women (6515 in Europe), and randomized 8901 each to rosuvastatin 20 mg daily and placebo. At baseline, 9% of the cohort was considered to be at 'high risk' for a first cardiovascular event on the basis of having a 10-year Framingham risk of MI/coronary death above 20%; 52% were considered to be at 'high risk' on the basis of having a 10-year SCORE risk of cardiovascular death of 5% or higher using the extrapolated model, and 35% were considered to be at 'high risk' using the

capped SCORE model. Baseline characteristics of these high-risk patients are shown by treatment allocation (Table 1). As anticipated, when compared with the entire JUPITER cohort, the higher-risk patients were older, more often male and more likely to smoke, have hypertension and low levels of HDL-C. Differences between the high-risk Framingham and SCORE groups reflect the patient characteristics included in the risk algorithms and their weighted contribution to individuals' estimated global cardiovascular risk. In particular, metabolic syndrome was more prevalent among high-risk Framingham patients.

For the entire JUPITER cohort, rosuvastatin lowered LDL-C by 50%, triglycerides by 17% and hs C-reactive protein by 37%, whereas it increased HDL-C by 4% compared with placebo ($P < 0.001$ for all from baseline to year 1).¹ In the high-risk groups, effects of rosuvastatin on lipoproteins and hs C-reactive protein were similar to those seen for the entire cohort (Table 2), with significant reductions in LDL-C, triglycerides, and hs C-reactive protein ($P < 0.0001$ vs. placebo for all) and a significant increase in HDL-C ($P < 0.0001$).

At study closure (median follow-up 1.8 years; maximal follow-up 5 years), the occurrence of MI/stroke/cardiovascular death was lower among high-risk subjects allocated to rosuvastatin compared with placebo (HR: 0.50, 95% CI: 0.27–0.93 for Framingham risk score $>20\%$; HR: 0.57, 95% CI: 0.43–0.78 for SCORE risk $\geq 5\%$ extrapolated model; HR: 0.47, 95% CI: 0.32–0.68 for SCORE risk

$\geq 5\%$ capped model; Figure 1, Table 3). The proportional reduction in MI/stroke/cardiovascular death with rosuvastatin was similar for patients with Framingham risk score above or below 20% (P for interaction = 0.95), or SCORE risk above or below 5% (P for interaction = 0.37 capped model, 0.25 extrapolated model).

Rosuvastatin significantly reduced the occurrence of the primary composite endpoint of MI/stroke/arterial revascularization/unstable angina/cardiovascular death as well as fatal/non-fatal MI and fatal/non-fatal stroke among patients with SCORE $\geq 5\%$ (in both the extrapolated and capped models; Table 3, Figure 2) and reduced all-cause mortality in the capped SCORE model (Table 3).

In the higher-risk patients, there was no evidence of heterogeneity for the endpoint of MI/stroke/cardiovascular death in subgroups by gender, age, race/ethnicity, hypertension, smoking, family history of premature coronary heart disease, baseline HDL-C, or C-reactive protein (Figure 3). Patients with body mass index $>30 \text{ kg/m}^2$ at baseline appeared to benefit less from rosuvastatin treatment compared with non-obese patients, but this interaction between treatment assignment and body mass index was not observed for the JUPITER cohort as a whole and thus is likely to be more apparent than real.

In the high-risk patients, serious adverse events were reported with similar frequency in rosuvastatin and placebo-allocated patients (Table 4). A small excess of myalgia was reported with rosuvastatin in patients with Framingham risk score $>20\%$

Table 1 Baseline characteristics according to the estimated 10-year risk defined by the Framingham risk score or the systematic coronary risk evaluation risk algorithm

	Entire cohort	Framingham 10-year risk $>20\%$		SCORE 10-year risk $\geq 5\%$			
		Rosuvastatin	Placebo	Extrapolated model		Capped model	
				Rosuvastatin	Placebo	Rosuvastatin	Placebo
<i>n</i>	17 802	786	772	4619	4683	3130	3177
Age (years)	66	74	74	70	70	67	67
Female (%)	38	17	15	32	31	12	11
Race or ethnic group (%)							
White	71	68	67	72	72	74	74
Black	13	15	14	14	14	14	14
Hispanic	13	14	17	10	10	7	7
Other	4	2	2	2	3	4	4
Hypertension (%)	57	87	86	67	67	69	68
Current smoker (%)	16	32	31	21	22	30	31
Family history premature CHD ^a (%)	12	8	11	10	10	10	10
HDL-C $< 1.0 \text{ mmol/L}$ (%)	23	60	60	22	22	24	24
Body mass index (kg/m^2)	28	28	28	28	28	28	28
Metabolic syndrome ^b (%)	41	68	69	41	41	40	40
Framingham 10-year risk score	10	25	25	16	16	16	16
SCORE 10-year risk	5	14	14	9	9	10	10

Values are median or *n* (%). SCORE, systematic coronary risk evaluation; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol.

^aCHD in a male first-degree relative before age 55 or in a female first-degree relative before age 65.

^bMetabolic syndrome defined as three or more of the following: waist circumference $>102 \text{ cm}$ (men) and 89 cm (women); triglycerides $\geq 1.7 \text{ mmol/L}$; HDL-C $< 1.0 \text{ mmol/L}$ (men) and 1.3 mmol/L (women); blood pressure $\geq 85 \text{ mmHg}$ diastolic or 130 mmHg systolic or treated hypertension; fasting glucose $\geq 5.6 \text{ mmol/L}$.

Table 2 Lipoprotein and high-sensitivity C-reactive protein levels in high-risk subgroups

	Framingham 10-year risk >20%		SCORE 10-year risk $\geq 5\%$			
			Extrapolated model		Capped model	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo
LDL-C (mmol/L)						
Baseline	2.8 (2.5–3.1)	2.8 (2.5–3.1)	2.8 (2.5–3.1)	2.8 (2.5–3.1)	2.8 (2.5–3.1)	2.8 (2.5–3.1)
Year 1	1.3 (1.1–1.9)	2.8 (2.4–3.2)	1.4 (1.1–1.8)	2.8 (2.4–3.2)	1.4 (1.1–1.9)	2.8 (2.4–3.2)
% change	–51	0	–49	+2	–49	+2
P-value	<0.0001		<0.0001		<0.0001	
Non-HDL-C (mmol/L)						
Baseline	3.7 (3.3–4.0)	3.7 (3.3–4.0)	3.5 (3.1–3.87)	3.5 (3.1–3.8)	3.5 (3.1–3.8)	3.5 (3.1–3.8)
Year 1	2.0 (1.7–2.6)	3.6 (3.2–4.1)	2.0 (1.6–2.5)	3.5 (3.0–4.0)	2.0 (1.7–2.5)	3.5 (3.0–4.0)
% change	–45	0	–43	+2	–42	+2
P-value	<0.0001		<0.0001		<0.0001	
HDL-C (mmol/L)						
Baseline	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Year 1	1.1 (1.0–1.3)	1.0 (0.9–1.2)	1.3 (1.1–1.7)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.3 (1.0–1.6)
% change	+9	+3	+6	0	+6	0
P-value	<0.0001		<0.0001		<0.0001	
Triglycerides (mmol/L)						
Baseline	1.7 (1.3–2.5)	1.7 (1.2–2.5)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	1.3 (0.9–1.9)
Year 1	1.3 (1.0–1.8)	1.6 (1.2–2.4)	1.1 (0.8–1.5)	1.3 (1.0–1.8)	1.1 (0.8–1.6)	1.3 (1.0–1.9)
% change	–22	–3	–16	0	–16	+1
P-value	<0.0001		<0.0001		<0.0001	
hs C-reactive protein (mg/L)						
Baseline	4.6 (3.0–7.9)	4.6 (3.1–7.8)	4.2 (2.9–7.1)	4.4 (2.9–7.3)	4.2 (2.8–6.9)	4.4 (2.9–7.2)
Year 1	2.5 (1.3–4.8)	3.7 (2.3–6.7)	2.3 (1.3–4.6)	3.6 (2.0–6.4)	2.2 (1.2–4.5)	3.5 (2.0–6.4)
% change	–49	–17	–46	–21	–46	–21
P-value	<0.0001		<0.0001		<0.0001	

Values are median (interquartile range) or median (%); SCORE, systematic coronary risk evaluation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs, high sensitivity.

(rosuvastatin 5.9% and placebo 5.3%) or SCORE risk $\geq 5\%$ (rosuvastatin 7.9%, placebo 6.5% for the extrapolated model; 7.4 vs. 5.8% for the capped model). Myopathy, myositis, and rhabdomyolysis were reported with similar frequency in the two treatment groups. In the entire JUPITER cohort, investigator-reported diabetes, a non-adjudicated outcome, was more frequent with rosuvastatin (rosuvastatin 3.0% and placebo 2.4%; $P = 0.01$).¹ Investigator-reported diabetes was not consistently more frequent with rosuvastatin in the higher-risk patients (HR: 0.70, 95% CI: 0.41–1.19, $P = 0.19$ for Framingham risk score $>20\%$; HR: 1.11, 95% CI: 0.86–1.43, $P = 0.43$ for extrapolated SCORE risk $\geq 5\%$; HR: 0.99, 95% CI: 0.72–1.36, $P = 0.95$ for capped SCORE risk). At 2 years following randomization, a 0.1% greater increase in glycosylated haemoglobin was observed with rosuvastatin compared with placebo ($P < 0.001$ vs. placebo for the high-risk groups). However, on-treatment fasting glucose levels were similar in the two treatment groups ($P = 0.95$ vs. placebo for Framingham risk score $>20\%$; $P = 0.19$ for extrapolated SCORE risk $\geq 5\%$; $P = 0.52$ for the capped SCORE model).

Discussion

JUPITER investigated the effect of rosuvastatin 20 mg daily compared with placebo on major cardiovascular events in a population not requiring treatment under guidelines in effect in 2003,^{9,11} but at an increased cardiovascular risk on the basis of age and elevated hs C-reactive protein. To provide European practitioners access to *post hoc* subgroup data that were influential to the European health authorities, in this analysis, we limited the target population to select an even higher risk group using two global risk assessment algorithms, Framingham and SCORE. In these higher risk subgroups, rosuvastatin lowered LDL-C, triglycerides, and hs C-reactive protein and raised HDL-C, consistent with effects observed for the entire cohort. Rosuvastatin reduced the risk of the composite endpoint of MI/stroke/cardiovascular death by 50% in the high-risk Framingham group ($P = 0.028$ vs. placebo), 43% in the high-risk SCORE group using the extrapolated model ($P = 0.0003$) and 53% ($P < 0.0001$) using the capped model, consistent with the 47% reduction observed for the entire cohort.¹

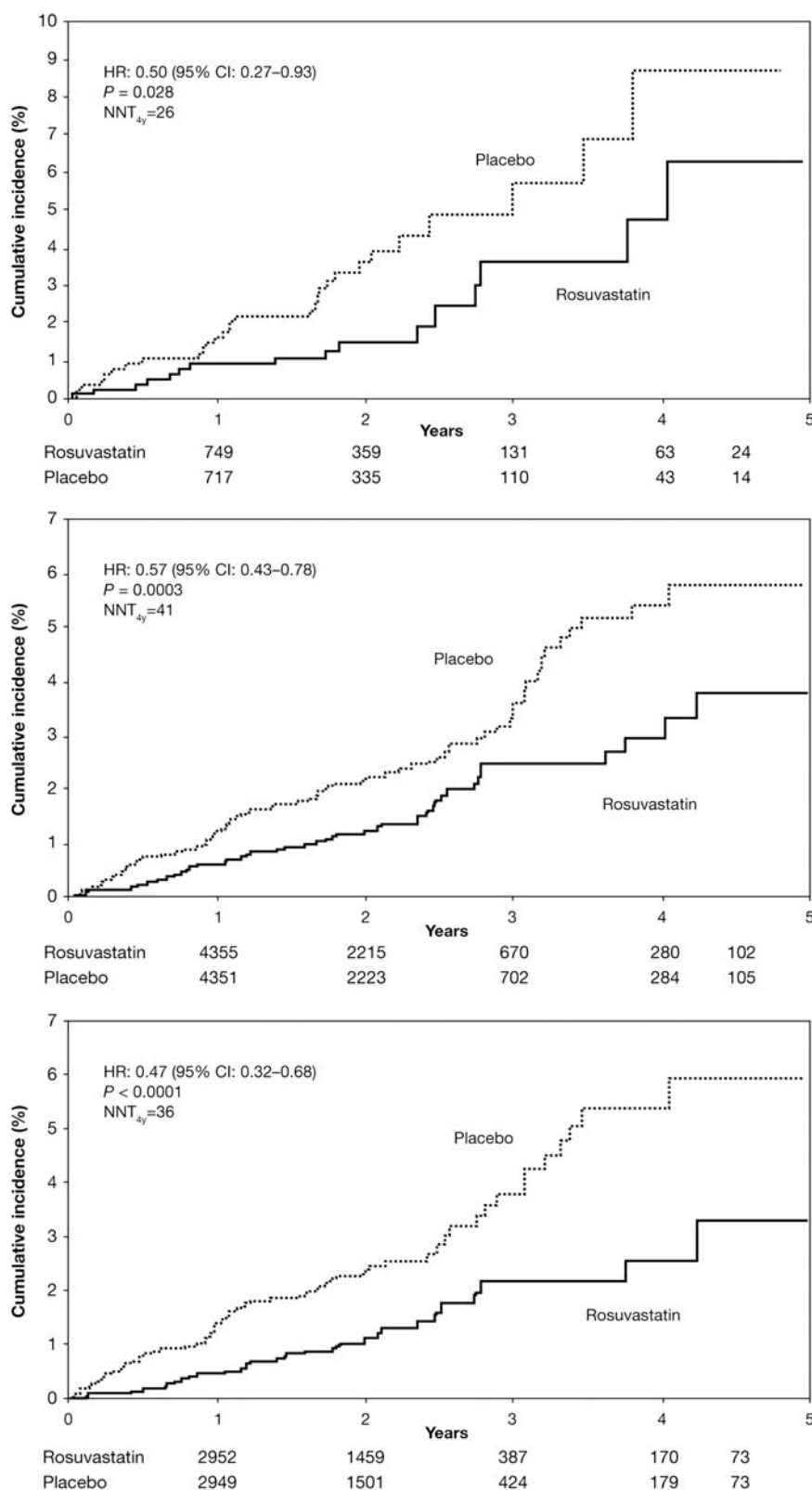


Figure 1 Cumulative incidence of myocardial infarction/stroke/cardiovascular death in high-risk patients. The cumulative incidence of myocardial infarction/stroke/cardiovascular death is shown by the treatment group for patients with a 10-year Framingham risk score $>20\%$ (upper panel), 10-year systematic coronary risk evaluation risk $\geq 5\%$ using the extrapolated model (middle panel), and systematic coronary risk evaluation risk $\geq 5\%$ using the capped model (lower panel). NNT, number needed to treat.

Table 3 Major cardiovascular events and all-cause mortality in high-risk subgroups

	Rosuvastatin		Placebo		ARR	HR (95% CI)	P-value
	No. events	Event rate ^a	No. events	Event rate			
Entire JUPITER cohort (n = 8901 rosuvastatin, 8901 placebo)							
Primary endpoint	142	7.7	251	13.6	5.9	0.56 (0.46–0.69)	<0.0001
MI/stroke/CV death	83	4.5	157	8.5	4.0	0.53 (0.40–0.69)	<0.0001
Total mortality	198	10.0	247	12.5	2.5	0.80 (0.67–0.97)	0.02
Baseline Framingham >20% (n = 786 rosuvastatin, 772 placebo)							
Primary endpoint	29	17.2	38	24.1	6.9	0.70 (0.43–1.14)	0.155
MI/stroke/CV death	16	9.4	29	18.2	8.8	0.50 (0.27–0.93)	0.028
Total mortality	31	17.2	40	23.6	6.3	0.73 (0.46–1.17)	0.193
Baseline SCORE ≥5% (extrapolated model; n = 4619 rosuvastatin, 4683 placebo)							
Primary endpoint	111	11.5	183	18.8	7.3	0.61 (0.48–0.78)	<0.0001
MI/stroke/CV death	67	6.9	118	12.0	5.1	0.57 (0.43–0.78)	0.0003
Total mortality	149	14.4	185	17.5	3.2	0.82 (0.66–1.02)	0.076
Baseline SCORE ≥5% (age capped at 65 years; n = 3130 rosuvastatin, 3177 placebo)							
Primary endpoint	71	11.1	130	20.1	9.0	0.56 (0.42–0.74)	<0.0001
MI/stroke/CV death	38	5.9	83	12.7	6.9	0.47 (0.32–0.68)	<0.0001
Total mortality	97	15	135	20.6	5.6	0.74 (0.57–0.96)	0.022

MI, myocardial infarction; CV, cardiovascular; HR, hazard ratio; CI, confidence interval; SCORE, systematic coronary risk evaluation; ARR, absolute rate reduction. Primary endpoint, time to occurrence of first MI/stroke/cardiovascular death/arterial revascularization/unstable angina.

Data for the entire JUPITER cohort are from reference 1. Extrapolated and capped SCORE models are described in the 'Methods' section.

^aRates are per 1000 person-years.

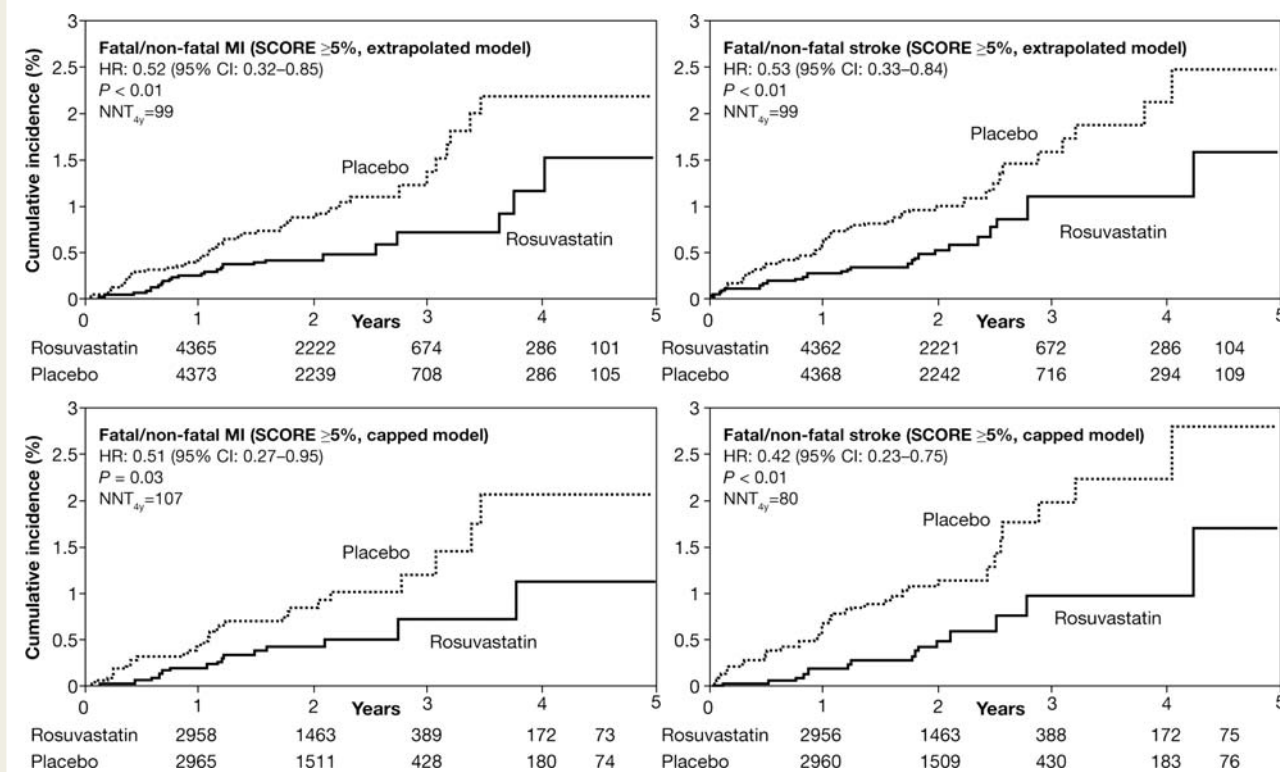


Figure 2 Cumulative incidence of fatal/non-fatal myocardial infarction and stroke in high-risk patients. The cumulative incidence of fatal/non-fatal myocardial infarction and fatal/non-fatal stroke are shown by the treatment group among patients with a 10-year systematic coronary risk evaluation risk ≥5% using the extrapolated (upper panel) and capped models (lower panel).

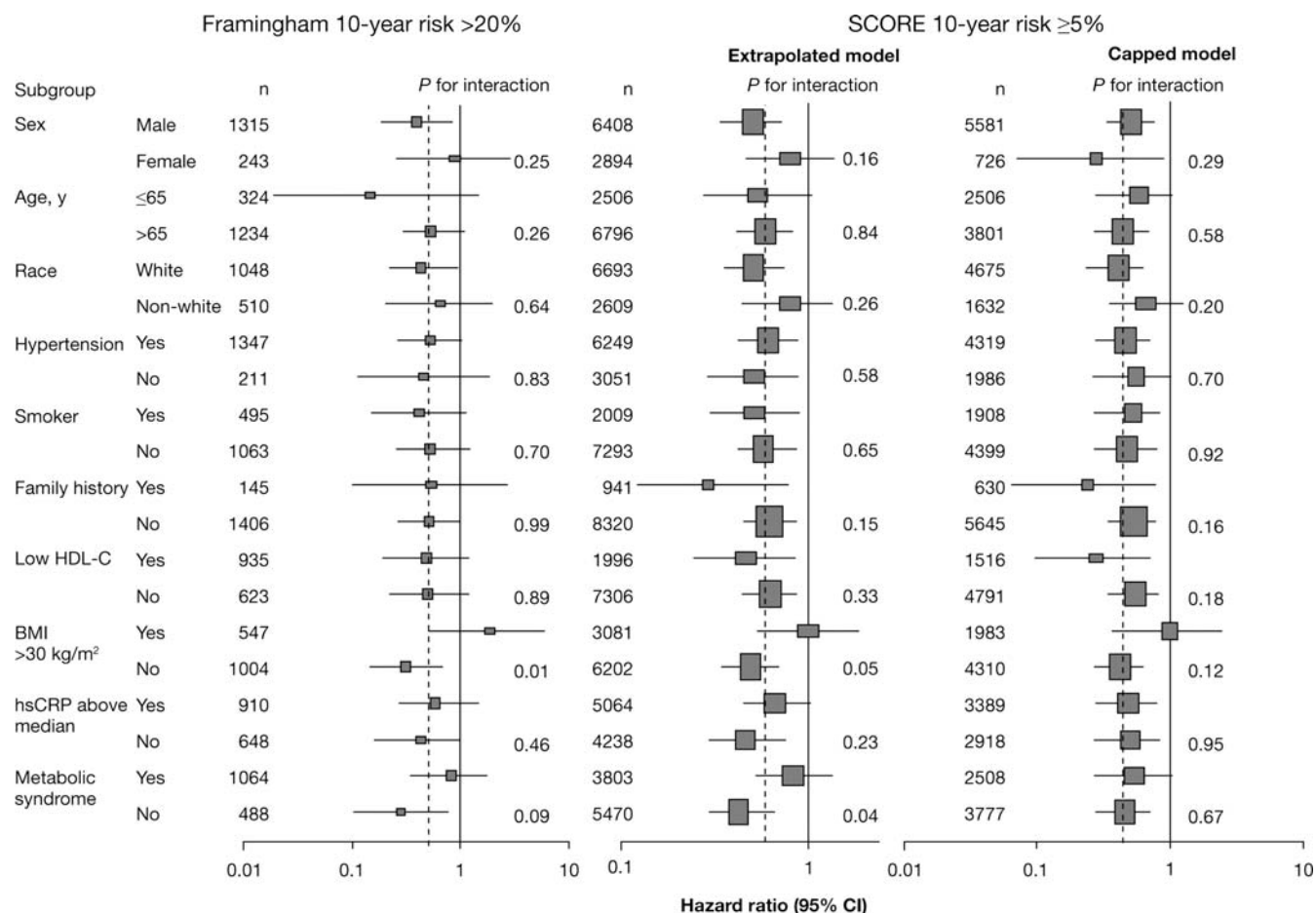


Figure 3 Effects of rosuvastatin on myocardial infarction/stroke/cardiovascular death in high-risk patients, according to baseline characteristics. The hazard ratios and 95% confidence intervals for rosuvastatin when compared with placebo are shown for patients with Framingham risk score >20% and systematic coronary risk evaluation risk ≥5% (extrapolated and capped models). Size of the point estimate rectangle is proportional to the number of clinical events. The dashed vertical line indicates the relative risk reduction for the entire trial cohort. Also shown are P-values for the test of an interaction between the composite endpoint and categories within each subgroup.

Table 4 Adverse events and laboratory abnormalities in high-risk subgroups

	Framingham risk >20%		SCORE risk $\geq 5\%$			
	RSV	Placebo	Extrapolated model		Capped model	
			RSV	Placebo	RSV	Placebo
<i>n</i>	786	772	4619	4683	3130	3177
Any adverse event	626 (79.6)	617 (79.9)	3681 (79.7)	3704 (79.1)	2490 (79.6)	2510 (79.0)
Any serious adverse event	154 (19.6)	153 (19.8)	855 (18.5)	878 (18.7)	544 (17.4)	587 (18.5)
Muscle symptoms						
Myalgia	46 (5.9)	41 (5.3)	363 (7.9)	303 (6.5)	233 (7.4)	183 (5.8)
Myositis	0	1 (0.1)	3 (0.1)	3 (0.1)	3 (0.1)	2 (0.1)
Myopathy	0	0	0	1 (0)	0	1 (0)
Rhabdomyolysis	0	0	1 (0)	0	1 (0)	0
Newly diagnosed cancer	35 (4.5)	39 (5.1)	195 (4.2)	212 (4.5)	116 (3.7)	145 (4.6)
Death from cancer	9 (1.1)	11 (1.4)	29 (0.6)	48 (1.0)	19 (0.6)	40 (1.3)
Gastrointestinal disorder	206 (26.2)	214 (27.7)	1184 (25.6)	1175 (25.1)	763 (24.4)	737 (23.2)
Renal disorder	100 (12.7)	87 (11.3)	487 (10.5)	523 (11.2)	355 (11.3)	354 (11.1)
Hepatic disorder	19 (2.4)	14 (1.8)	103 (2.2)	101 (2.2)	65 (2.1)	57 (1.8)
Investigator-reported diabetes	24 (3.1)	34 (4.4)	131 (2.8)	116 (2.5)	84 (2.7)	83 (2.6)
Laboratory values						
Creatinine >100% increase from baseline [<i>n</i> (%)]	1 (0.1)	0	7 (0.2)	3 (0.1)	6 (0.2)	2 (0.1)
eGFR at 12 months (mL/min/1.73 m ²)	65.0 (14.2)	64.4 (13.9)	66.9 (14.2)	66.4 (13.6)	69.2 (14.3)	68.7 (13.3)
ALT >3x ULN on consecutive visits [<i>n</i> (%)]	3 (0.4)	2 (0.3)	14 (0.3)	6 (0.1)	12 (0.4)	5 (0.2)
HbA _{1c} at 24 months (%)	6.02 (0.53)	5.92 (0.53)	5.96 (0.49)	5.86 (0.46)	5.97 (0.48)	5.87 (0.46)
Fasting glucose at 24 months (mmol/L)	5.7 (0.9)	5.7 (1.3)	5.6 (1.1)	5.6 (0.9)	5.6 (1.0)	5.6 (0.9)

Values are *n* (%) or mean (standard deviation). SCORE, systematic coronary risk evaluation; RSV, Rosuvastatin; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; HbA_{1c}, glycosylated haemoglobin; ULN, upper limit of normal.

Adverse events and laboratory abnormalities were consistent with the known safety profile of rosuvastatin.¹²

Strengths of this analysis include the randomized, placebo-controlled design, broad geographic representation including a substantial number of Europeans, and inclusion of large numbers of women and ethnic minority participants. A limitation is the *post hoc* selection of the higher risk subgroups, which was undertaken in response to health authority requests.⁴ For example, analysis of JUPITER subgroups by SCORE strata was not pre-specified and since SCORE by design is limited to those under age 65, we needed to extrapolate findings for the many JUPITER participants over this age cut-off that clearly benefited from rosuvastatin.¹³ The subgroups by baseline characteristics in Figure 3 are drawn from within the subgroups of high-risk patients; as such, limited conclusions can be drawn from these data. Neither the Framingham nor the SCORE models include hs C-reactive protein evaluation; as all participants in JUPITER had hs C-reactive protein levels >2 mg/L and as elevated hs C-reactive protein has been shown to have a magnitude of risk prediction at least as large as that of elevated cholesterol,¹⁴ it is likely that both the Framingham and the SCORE systematically underestimate the true risk of JUPITER participants.

Also in keeping with health authority requests, the analyses here used a composite endpoint of MI/stroke/cardiovascular death

rather than the pre-specified JUPITER primary endpoint. Nonetheless, the relative reduction in MI/stroke/cardiovascular death with rosuvastatin was remarkably consistent across a range of baseline participant characteristics and consistent with primary trial analyses of the full study population as pre-specified in the JUPITER protocol. Global risk prediction scores can be used to direct use of preventive therapies such as statins towards patients most likely to benefit.^{15,16} As expected, clinical event rates in the JUPITER placebo group were higher in the high-risk Framingham or SCORE groups compared with the entire cohort for the primary study endpoint as well as for the composite of MI/stroke/cardiovascular death and all-cause mortality. The magnitude of the absolute rate reduction for clinical events was correspondingly greater in the high-risk groups (Table 3).

Two factors contributing to the observed absolute reduction in clinical events in JUPITER were the underlying event rate in the placebo group, enhanced in this case by selecting patients with high global cardiovascular risk and elevated hs C-reactive protein, and the relative risk reduction due to treatment, enhanced by use of a high-efficacy statin. The reductions in LDL-C (49%) and clinical events (43–53% for MI/stroke/cardiovascular death) with rosuvastatin in the JUPITER patients with SCORE risk $\geq 5\%$ are greater than reported for other statins.^{17,18} Although these data support the use of high-efficacy statin therapy, they do not

minimize the roles of diet, exercise, and smoking cessation as the most important interventions for primary prevention. Despite the benefit derived from treatment with rosuvastatin in these high-risk patients, caution should be exercised when considering treatment of patients lacking any cardiovascular risk factors. Further, long-term compliance with statin therapy is critical for efficacy among those patients where pharmacologic therapy is indicated in addition to lifestyle interventions.

Although the analyses presented here parallel those requested by European Health Authorities, they do not address most patients actually studied in the JUPITER trial. For example, among the 7340 men and women with elevated hs C-reactive protein and the Framingham risk scores of 11–20%, where the 4.5-year absolute risk of a primary endpoint was 10.6% in the placebo group, rosuvastatin was associated with a 49% reduction in risk (HR: 0.51, 95% CI: 0.39–0.68, $P < 0.0001$). Similarly, among the 6091 participants with entry Framingham scores of 5–10%, where the 4.5-year absolute risk was 5.3%, a 45% reduction was observed with rosuvastatin (HR: 0.55, 95% CI: 0.36–0.84, $P = 0.005$), and among trial participants with elevated hs C-reactive protein with SCORE risk $< 5\%$, rosuvastatin was associated with a 56% reduction in vascular risk (HR: 0.44, 95% CI: 0.29–0.68). Thus, the JUPITER trial data also indicate that many individuals with elevated hs C-reactive protein who fall outside 'high-risk' subgroups defined by either Framingham or SCORE have both substantive absolute risk and large relative risk reductions when treated with rosuvastatin.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: During the period of this project, W.K. reports receiving research support grants from Dade–Behring and GlaxoSmithKline; lecture fees from AstraZeneca, Pfizer, Novartis, and Boehringer-Ingelheim; and consulting fees from GlaxoSmithKline and Roche. P.M.R. reports having received investigator-initiated research grant support from the National Heart Lung and Blood Institute, the National Cancer Institute, the Donald W Reynolds Foundation, the Leducq Foundation, AstraZeneca, Novartis, Merck, Abbott, Roche, and sanofi-aventis; consulting fees from AstraZeneca, Novartis, Merck, Merck-Schering Plough, sanofi-aventis, ISIS, Seimens, and Vascular Biogenics; and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Seimens and AstraZeneca.

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